REMARKS

Claims 1-3, 9-11, 15, 17, 21, and 22 are pending in the application and were examined in the present Office Action; claims 4-8, 12-14, 16, 18-20, and 23-27 stand cancelled without prejudice or disclaimer pursuant to the Restriction Requirement. Claims 3 and 9 stand canceled in this amendment without prejudice or disclaimer, Applicants reserving the right to prosecute the subject matter of any or all of the canceled claims in related continuation or divisional applications. The amendments to the claims find support in the specification and claims as originally filed.

The amendments to claim 1 find support, for example, at page 3, line 26, page 6, lines 1-6, page 14, lines 21-27, original claim 9, and elsewhere in the specification and claims as originally filed.

The amendments to claims 2 and 17 clarify the claim language, and accord with the amendments to claim 1.

The amendments to claim 11 find support in the specification, for example, at page 18, lines 12-16, and elsewhere in the specification and claims as originally filed.

The amendments to claim 15 more clearly point out and distinctly claim the subject matter of the invention, and find support on page 6, lines 18-20, and elsewhere in the specification and claims as originally filed.

No new matter is added by the amendments.

The Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 2, 9-11, 15, 17, and 21-22 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner objects to the term "m" in claim 1.

Applicants note that as amended, the term "m" in claim 1 is defined per the definition of page 3, line 26 of the application as originally filed. Accordingly, Applicants

respectfully submit that the claims are not indefinite, and that the rejections of Claims 1, 2, 9-11, 15, 17, and 21-22 under 35 U.S.C. §112, second paragraph are overcome.

The Rejections under 35 U.S.C. § 112, first paragraph

Claims 11, 17, 21, and 22 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled by the disclosure of the specification. "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). Nonetheless, enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly excessive." Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). Applicants further note that the amount of guidance or direction needed to enable an invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art (*In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)), and it is well-recognized that the skill in the art of molecular biology is quite high (*Ex parte Forman*, 230 USPQ 546, 548 (Bd. Pat. App. & Int. 1986)).

As discussed below, Applicants submit that the specification discloses how to make and use the full scope of the claimed invention without undue experimentation.

Applicants acknowledge the Examiner's statement that the specification is "enabling for an isolated protein comprising the motif of '(**X1**)$_n$EVEKIKTTVKESATEEKLTPV**X2**L(**X3**) capable of modulating cellular proliferation or inhibiting cellular proliferation and a method of inhibiting cellular proliferation comprising the delivering to a target cell the said isolated peptide." However, the Examiner also suggested that the specification "does not reasonably provide enablement for a peptide capable of 'selectively inhibiting cancerous cells' or for a method of inhibiting cellular proliferation comprising delivering a nucleic acid encoding said protein." Applicants respectfully disagree with these suggestions.

Selective Inhibition

Applicants note that the specification discusses inhibition of cancer cells at length, including selective inhibition of cancer cell, for example, at pages 6, lines 12-14 and 21-30, page 12, lines 11-27, page 18, lines 11-29, page 30, lines 25-26, and elsewhere in the specification. Applicants submit that the rejections under 35 U.S.C. §112, first paragraph, with respect to the phrase "selectively inhibiting cancerous cells" are overcome in view of the Examiner's agreement that the specification is specification is "enabling for an isolated protein ... capable of modulating cellular proliferation or inhibiting cellular proliferation and a method of inhibiting cellular proliferation" and in view of the amendment eliminating the word "selectively" from claim 11.

Nucleic Acid Delivery

Applicants note that the specification discusses delivery of nucleic acid message to cells, for example, at pages 6, lines 15-17, page 15, lines 15-30, page 18, lines 30-31, and pages 19, 20 and 21 (lines 1-2), and demonstrates delivery of message encoding a claimed peptide to, and expression in, cells, as disclosed in Example 1 at pages 25-28. Thus, Applicants provide an example of nucleic acid delivery.

In addition, Applicants discuss at length methods for nucleic acid delivery sufficient to enable one of ordinary skill in the art to practice the invention without undue experimentation. Applicants agree, as noted by the Examiner under the heading "The nature of the invention," that the invention is in the class of biology, and agree with the Examiner that the level of skill in the art is high. The Examiner suggests, however, that the claims be interpreted to "read on peptides capable of selectively targeting and treating cancerous cells only without affecting non-cancerous cells as well as a method involving gene therapy." Applicants note that the claims, particularly as amended in the present Amendment, are directed to methods for inhibiting cellular proliferation in target cells, and so should not be interpreted as suggested by the Examiner. Claim 11 now refers to a peptide capable of inhibition of proliferation of cancerous cells, and does not include the word "selective." Claims 17, 21 and 22, directed to methods for inhibiting cellular proliferation comprising delivering an effective amount of a nucleic acid to a target cell, can indeed include inhibiting cellular proliferation in a patient, but do not

explicitly recite the words "gene therapy" (see, *e.g.*, page 18, lines 30 and 31 to page 19, lines 1-8).

Although the Examiner notes that "the treatment of cancer in general is at most unpredictable" (page 5, line 6 of the Office Action under reply), Applicants note that the claimed invention is directed, for example, to methods for inhibiting cellular proliferation, by delivering an effective amount of a peptide of claim 1 or nucleic acid encoding it to a target cell. Although the Examiner provides an extensive discussion of pessimistic assessments of cancer treatments and of gene therapy published several years prior to the filing date of the present application, citing statements from 1995 and 1997, for example, Applicants submit that the disclosed methods for delivering nucleic acids to target cells were well known and well within the skill of one of ordinary skill in the art at the time of filing in 2001.

The Examiner cites a reference published about the time the present application was filed (Rubanyi (2001)) as stating that "convincing clinical efficacy could not be demonstrated yet in most trials conducted so far" (page 6, lines 16-17 of the Office Action under reply). However, Applicants note that Rubanyi discusses "the recent report of successful gene therapy in SCID-XI patients (Cavazzana-Calvo et al., 2000), and the success in hemophilia B patients receiving factor IX therapy delivered by adeno-associated viral vectors (Kay et al., 2000)" (Rubanyi, page 115, lines 2-4) demonstrating that the state of the art at the time the application was filed included successful delivery of nucleic acid message in patients. It was known in the art that delivery of genetic message to target cells had indeed been accomplished, as may be seen by Rubanyi's further remarks, for example, discussing the "encouraging results so far" for therapeutic angiogenesis (at page 133, line 37, referring to the discussion of preclinical and clinical studies of "intracoronary injections of recombinant, replication incompetent adenovirus 5 carrying a potent and secreted angiogenic growth factor gene" on pages 132-133-42).

Thus, the Examiner's comments on pages 5-7 under the heading "The unpredictability of the art and the state of the prior art" are believed to be more properly

directed to the "prior" art, that is, the state of the art several years before the filing date of the present application. Applicants note that the one reference dated from about the time of the present application provides confirmation that delivery of nucleic acid to target cells had indeed been performed in several instances. Thus, one of ordinary skill in the art, at the time the application was filed, would be able to make and use the claimed invention based on the disclosure and the general knowledge of one of ordinary skill in the art at the time.

The Examiner correctly notes that a working example is provided.

The Examiner suggests that no guidance is provided for a peptide that is "capable of "selectively" target cancerous cells or a method of gene therapy." Applicants note that the present claims do not refer to selective targeting of cancerous cells, nor do any claims recite the phrase "gene therapy." Claims 17, 20 and 21 recite the delivery, to a target cell, of "an effective amount of ... a nucleic acid encoding the amino acid sequence of said peptide" where introduction of the peptide into a cell has been disclosed as leading to inhibiting cellular proliferation. As discussed above, one of ordinary skill in the art, in view of the disclosure and the knowledge in the art at the time, would know how to deliver an effective amount of nucleic acid, and so to inhibit cellular proliferation in the target cells, as required by the claims.

Accordingly, in view of the above, including in view of the amount of disclosure, including the working example, the methods claims being directed to inhibiting cellular proliferation in target cells, the high level of skill in the art, and the success in the art for delivering nucleic acid message to target cells, Applicants submit that the rejections under 35 U.S.C. §112, first paragraph, with respect to nucleic acid delivery are overcome.

The Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 9-11, 17, 21, and 22 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. § 112, first paragraph is whether the disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." In re Kaslow, 707 F.2d 1366, 1375, 212 USPQ 1089, 1096 (Fed. Cir. 1983); see also Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Union Oil v. Atlantic Richfield Co., 208 F.3d 989, 996 (Fed. Cir. 2000).

The present claims are directed to an isolated peptide, and variants and fragments of the isolated peptide, and methods for using these peptides, variants and fragments. The Written Description Guidelines (The Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, & 1, 'Written Description' Requirement, 66 F.R. 1099, 1106 (January 5, 2001)) discuss peptides, variants and fragments. Example 14 of the Written Description Guidelines issued by the U.S. Patent Office clearly states that "protein variants meets the requirements of 35 U.S.C.§112, first paragraph as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins is routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence". Based on these guidelines, Applicants submit that the instant specification evidences the actual reduction to practice of the claimed peptides. In addition, the specification provides detailed description about the variants and fragments of the peptide, and of its functional effects. Thus, Applicants submit that the genus of peptides of claim 1, and of nucleic acids that code for it, and variants and fragments with 95% similarity and further, which possess the functional property that it is "capable of modulating cellular proliferation" meet the requirements of 35 U.S. C. §112, first

paragraph as providing adequate written description and demonstrate that Applicants had possession of the claimed invention at the time the application was filed.

Accordingly, Applicants have conveyed with reasonable clarity to those skilled in the art, as of the filing date sought, that they were in the possession of the invention as of that date, and Applicants thus respectfully submit that the rejections of Claims 1, 9-11, 17, 21, and 22 under 35 U.S.C. §112, first paragraph are overcome.

The Rejections under 35 U.S.C. §102

Claims 1, 2, 9, 10, 11, 15, 17, 21, and 22 stand rejected under 35 U.S.C. § 102 as allegedly anticipated by Rosen *et al.*, WO 00/55173 (hereafter, "Rosen"). Claims 1, 2, and 9-11 stand rejected under 35 U.S.C. § 102 as allegedly anticipated by Echeverri *et al.*, J. Cell. Biol. 132:617-633 (1996) (hereafter, "Echeverri"). Applicants respectfully traverse these rejections.

Anticipation under 35 U.S.C. § 102 requires that "every element of the claimed invention be identically shown in a single reference." (*In re Bond*, 910 F.2d 831,832 (Fed. Cir. 1990).

Applicants note that the peptide of claim 1 includes a modified amino acid residue that is selected from a protected amino terminal amino acid, a protected carboxy terminal amino acid, and an amino acid having an added fatty-acid or an polyisoprenoid side chain. Applicants further note that Rosen fails to discuss a peptide of claim 1 that includes a modified amino acid residue, and that Echeverri fails to discuss a peptide of claim 1 that includes a modified amino acid residue.

Moreover, neither Rosen nor Echeverri discuss an isolated peptide having an amino acid sequence as recited in claim 1, nor a nucleic acid encoding such an isolated peptide having such an amino acid sequence. Neither reference teaches that an isolated peptide having such an amino acid sequence is effective to modulate or inhibit cellular proliferation.

Accordingly, in the absence of any direct or indirect disclosure regarding the claimed peptides, or nucleic acids encoding the claimed isolate peptides, and in the absence of disclosure of the functional characteristics of such peptides, Applicants respectfully submit that claims 1, 2, 9, 10, 11, 15, 17, 21, and 22 are not anticipated by Rosen and recite allowable subject matter.

Similarly, Echeverri also failing to disclose the claimed peptides, or nucleic acids encoding the claimed isolate peptides, and failing to disclose the functional characteristics of such peptides, Applicants respectfully submit that claims 1, 2, and 9-11 are not anticipated by Echeverri and recite allowable subject matter. Applicants respectfully submit that the rejections under 35 U.S.C. § 102 are overcome.

CONCLUSION

Applicants respectfully submit that all pending claims are in condition for allowance, and respectfully request their reconsideration and allowance. Early notification of the allowance of the application is respectfully requested.

The Examiner is invited to contact the undersigned attorney at the telephone number indicated below should he find that there are any further issues outstanding.

Although no fees are believed to be due at this time, please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641** referencing Attorney's Docket No. **39754-0691 A**.

Respectfully submitted,

Dated: May 8, 2006

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